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A possible interaction of TIMP-1 and TSP-1 with familial mediterranean fever

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Abstract

Aim: Matrix metalloproteinases (MMPs) may influence many biological and pathological processes including inflammatory responses. Thrombospondins (TSP) are a glycoprotein group of the extracellular matrix. In this study, we aimed to investigate a possible association of TIMP-1 (an inhibitor of metalloproteinases) and TSP-1 (an adhesive protein involved in cell-matrix interactions) with familial Mediterranean fever. Material and Method: Thirty FMF patients who had compound heterozygous or homozygous MEFV mutations and thirty healthy controls were included in this study. The patients were selected after screening by reverse hybridization procedure. TIMP-1 and TSP-1 levels of the patients and controls were measured by ELIZA. Results: TIMP-1 and TSP-1 levels of the patients who had homozygous or compound heterozygous MEFV mutation were compared with 30 healthy controls. The levels of TIMP-1 in the patients were statistically higher than those in the control group ($p < 0.001$). There was no significant difference between the patients and controls in terms of TSP-1 levels ($p = 0.84$). Discussion: IL-1β has an important role in FMF disease and it may stimulate expression of TIMP-1. TIMP-1 levels are increased in FMF patients on the basis of inflammation and higher TIMP-1 levels in patients may be associated with the self-limited nature of FMF. TSP-1 level can be modulated by proinflammatory cytokines but there was no any significant difference between TSP-1 levels of FMF patients and the control group in our study. It can be thought that there is no interaction between TSP-1 and the pathogenesis of FMF.

Keywords

TIMP-1; TSP-1; FMF; Mutation

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive inflammatory disorder characterized by recurrent attacks of fever, peritonitis, pleuritis, abdominal pain, arthralgia and skin rash defined as erysipelas-like erythema [1]. It usually occurs in people of Mediterranean origin including Sephardic Jews, Arabs, Greeks, Armenians and Turks [2]. The cause of the disease is the mutations of MEFV gene (16p13.3) which is located on the short arm of chromosome 16 [3]. MEFV gene encodes a protein called pyrin (marenostrin) that is relevant to innate immunity [4]. MEFV mutations cause T helper 1 (Th1) polarization because the defective pyrin cannot prevent Th1 mediated inflammation [5]. Th1 cells are associated with the production of interferon-γ (IFN γ) and they are involved in immune responses against intracellular viral and bacterial infection [6].

Matrix metalloproteinases (MMPs) are a group of zinc-dependent enzymes which play an important role in degrading extracellular matrix [7, 8] and tissue remodeling both in various biological and pathological processes such as inflammatory and immune responses [9].

The MMP activities are inhibited by some specific endogenous inhibitors called tissue inhibitors of metalloproteinases (TIMPs) [10]. In this context, TIMPs have an important role in regulating extracellular matrix (ECM) turnover [11]. One of them, TIMP-1 is effective in extracellular matrix homeostasis and signaling pathways by inhibiting the activity of MMPs [12].

Some studies investigating the relationship between cytokines and matrix metalloproteinases have shown that plasma cytokines and acute phase proteins correlate positively with plasma MMP-9 or TIMP-1 [13]. Matrix metalloproteinases and Tissue inhibitors of metalloproteinases are expressed in the pleural fluid for various reasons and correlate with inflammatory mediators. It can be thought that the levels of TIMP-1 and TIMP-2 in the infectious pleural fluid may originate from their expression in resident mesothelial cells triggered by inflammatory mediators [14].

Thrombospondin-1 (TSP-1) is a multifunctional 450 kDa extracellular glycoprotein that is often stored in platelets [15]. It is an adhesive protein involved in cell–cell and cell–matrix interactions [16]. TSP-1 is a subunit of a disulfide-linked homotrimeric protein encoded by the THBS1 gene. The thrombospondin-1 protein is a matrix glycoprotein that has been reported to be an endogenous inhibitor of angiogenesis and tumor growth [17]. TSP-1 was discovered as a component of platelet alpha granules at first and it is secreted by many types of cells such as endothelial cells, monocytes, and fibroblasts. In the last decade, TSPs were identified as important mediators of neutrophil and monocyte chemotaxis, phagocytosis of neutrophils, regulation of T cell function [18].

In this study, we aimed to compare the levels of TIMP-1 and TSP-1 in FMF patients with those healthy controls and to evaluate the possible activities of these proteins in the presence of MEFV mutations.

Material and Method

A total of 86 patients diagnosed with FMF according to Tel Hashomer criteria and their families were screened for 12 MEFV gene mutations (E148Q, P369S, F479L, M680I(G/A), M680I(G/C), I692del, M694V, M694I, K695R, V726A, A744S, R761H) using Reverse Hybridization procedure (Vienna Lab, FMF StripAssay, GMBH, Austria). In molecular laboratory, total genomic DNA was extracted from peripheral blood samples of patients with DNA isolation kit (Invitec Invisorb Spin Blood Kit). Multiplex PCR amplification was performed using biotinylated primers. PCR products were incubated to nitrocellulose strips and the process was completed with color development and the detection of signals in Auto-LIPA (Auto-LIPA Innogenetics). We selected the patients who had compound heterozygous or homozygous mutation for ELIZA test. In this context, thirty FMF patients and thirty healthy controls were subjected to ELISA analysis. After MEFV mutation screening, the levels of TIMP-1 and TSP-1 were measured by ELISA test in both patients and control group. Statistical analysis was performed with SPSS 22.0 software. Mann-Whitney U test was used to assess the levels of these glycoproteins because the parametric test assumptions could not be met.

Results

All 86 patients diagnosed with FMF were screened for MEFV mutations. Only 34.9% of the patients (30 individuals) had homozygous or compound heterozygous mutation. Fourteen of these patients were female and sixteen were male. Other patients might suffer from FMF with a single mutation or more likely they had rare mutations that we could not screen. The most frequent mutation in the patients was M694V (36.7%). The rates of homozygous and compound heterozygous mutations were 40% and 60% respectively (Table 1).

Table 1. Mutation type of the patients.

Mutation	n	%
Homozygous		
M694V	6	20
E148Q	3	10
M680I (G/C)	2	6.7
V726A	1	3.3
Total	12	40
Compound hetero.		
E148Q+M694V	4	13.3
M680I (G/C)+M694V	3	10
V726A+M694V	2	6.7
E148Q+M680I (G/C)	2	6.7
M680I (G/C)+V726A	2	6.7
E148Q+P369S	2	6.7
R761H+M694V	1	3.3
E148Q+V726A	1	3.3
M680I (G/C)+R761H	1	3.3
Total	18	60

There were thirteen female and seventeen male in control group. There were no significant differences in the patients and control group in terms of sex. We measured TIMP-1 and TSP-1 levels of these thirty patients and thirty controls. There was a significant difference in the TIMP-I values between the patients and the control group ($p < 0.001$). The patients had higher TIMP-1 levels. On the other hand, there was no signifi-

cant difference between the TSP-1 levels of the patients and the control group (p = 0.85) (Table 2).

Table 2. The levels of TIMP-1 and TSP-1 in the patients and controls.

Parameter	Group	n	Mean (ng/ml)	Standard deviation	$\bar{x}$	Σ	U	Z	p
TIMP-1	Patients	30	577.75	106.34	44.20	1326.	39.	6.077	.000
	Controls	30	311.06	106.48	16.80	504.			
TSP-1	Patients	30	218.27	65.90	30.93	928.	437.	.192	.848
	Controls	30	218.90	75.86	30.07	902.			

Discussion

Familial Mediterranean fever (FMF) is a typical hereditary autoinflammatory disease characterized by periodic fever with arthritis and serositis. FMF patients have elevated serum levels of inflammatory cytokines and specific cytokines may be diagnostic biomarkers in attacks of FMF [19].

MMPs regulate several functions related to inflammation including bioavailability and activity of inflammatory cytokines and chemokines [20]. They play an important role in both pro- and anti-inflammatory pathways as regulatory enzymes [21]. The presence of these enzymes in some conditions such as cell migration, cell proliferation, apoptosis, and inflammation makes them common determinants of various pathological cases such as cancer, metastasis, and rheumatoid arthritis [22]. According to Hu et al., in an acute inflammation, blocking MMPs for a limited time interval might help to rescue critical tissues [23].

TIMP-1 is produced by a lot of cell types, such as peripheral blood monocytes and lymphocytes, airway macrophages and epithelial cells. In some studies, TIMP-1 was reported to be associated with several inflammatory conditions, including sepsis, community-acquired pneumonia, vasculitis and Kawasaki disease [24].

Pay et al. found that TIMP-1 levels in patients with osteoarthritis were also higher than in patients with Behcet's disease and familial Mediterranean fever. They suggest that the cause of lower levels of TIMP-1 in the patients with inflammatory arthritis may be the consumption of TIMP-1 in order to neutralize the increased levels of MMP-1 in joint spaces [25].

Kapsoritakis et al. declared that ulcerative colitis and Crohn's disease patients had significantly higher serum TIMP-1 levels when compared to healthy controls. There was an increased production of TIMP-1 in the patients of inflammatory bowel disease and this increase was correlated with the production of the well-known inflammatory markers called C reactive protein (CRP) and serum amyloid A (SAA) [26].

It has been shown that TIMP expression is associated with a variety of infectious and noninfectious inflammatory conditions. Lee et al. declared that TIMP-1-deficient mice were resistant to *Pseudomonas aeruginosa* corneal and pulmonary infections [27]. In a study by Mühl et al., TIMP-1 was significantly elevated in patients with severe sepsis on admission and started to decrease from the third day onward [28].

The association of TIMP-1 level with FMF is controversial. Dinç et al. found no significant difference between FMF patients and healthy subjects in terms of TIMP-1 levels [29]. IL-1β is involved in inflammatory manifestations of FMF [30]. In a study by Qu et al., it is claimed that IL-1β induces upregulation of MMPs and downregulation of TIMPs [31]. In this case, low levels of TIMP-1 may be expected in FMF patients but there are also different thoughts in the literature. Welser-Alves et al. showed that IL-1β promotes TIMP-1 expression in mixed glial cultures [32]. IL-1β may stimulate astrocytic expression of tissue inhibitor of metalloproteinases in mice [33]. On the other hand, Kapral et al. declared that proinflammatory cytokine IL-1β enhances MMP and TIMP mRNAs expression in colon cancer epithelial cells [34]. MEFV mutations in FMF patients are correlated with higher levels of secreted IL-1β. Increased secretion of IL-1β was observed not only in patients but also in the carriers [35]. Robert et al. suggested that pro-inflammatory mediators have complex effects in hepatic stellate cells via MMP/TIMP imbalance and IL-1 can stimulate hepatic cells to produce MMP-9, MMP-13, and TIMP-1, resulting in fibrogenesis [36].

On the basis of data obtained from various studies, we thought that there was a positive correlation between IL-1β and TIMP-1 in inflammatory processes. In our study, the levels of TIMP-1 in FMF patients were statistically higher than healthy controls. MMPs are normally expressed at low levels, but they rapidly increase during inflammatory processes. For example, Subtypes MMP-2 and MMP-9 are highly expressed in apical periodontitis and have been suggested to play an important role in the development of this disease [37]. In this context, the over-expression of MMPs in tissue may be closely associated with the severity of inflammation [38]. If matrix metalloproteinase activity contributes to inflammation, higher TIMP-1 levels in FMF cases may explain the self-limited nature of the disease. Thrombospondins are a family of extracellular matrix (ECM) proteins. Thrombospondin-1 is a calcium-binding glycoprotein involved in some biological functions such as wound repair, tumor growth and metastasis, angiogenesis, hemostasis, and inflammation [39].

TSP-1 stimulates endothelial cell apoptosis and inhibits endothelial cell migration and proliferation as an angiogenesis inhibitor [40].

Fordham et al. declared that TSP-1 modulates some components of the immune response at the sites of inflammation. It is associated with neutrophil and monocyte chemotaxis, phagocytosis, and the inhibition of angiogenesis [41]. Thrombospondin-1 (TSP-1) can be upregulated in various inflammatory diseases. Secretion of TSP-1 by endothelial cells can be modulated by proinflammatory cytokines such as TNFα and IL-1. For example, *in vitro* hantavirus infection of endothelial cells suppresses the transcription and accumulation of TSP-1 [42]. Previous studies suggest that interleukin-1β (IL-1) may have a major role in the pathogenesis of FMF [43]. Velasco et al. found the increase of IL-1β mRNA levels in the inflamed skin of TSP-1-deficient mice [44]. There may be a negative correlation between IL-1 β expression and the level of TSP-1. In this case, low levels of TSP-1 may be expected in FMF patients. Whereas, there was no significant difference in patients and controls in terms of the levels of TSP-1 in our study.

In conclusion, we detected higher TIMP-1 levels in FMF patients than in controls. IL-1β plays an important role in FMF disease and it stimulates expression of TIMP-1. It can be suggested

that TIMP-1 levels are elevated in FMF disease and it may contribute to limiting inflammation. On the other hand, we did not find any significant difference between TSP-1 levels of FMF patients and control group. We thought that there is no change in TSP-1 levels in FMF disease and TSP-1 does not contribute to the pathogenesis of FMF.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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